REMARKS

Status of the Claims

Claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 are currently pending in this application.

In this amendment, claim 77 has been canceled; claims 1, 78 and 79 have been amended to clarify the invention; and claims 81-86 have been added. Support for the amendment may be found in the application as originally filed, for example, at page 18, lines 18-28; page 31, lines 23-30; page 35, lines 20-23 (Example 3); page 36, lines 13-20 (Example 4) and pages 36-43 (Table 1). Thus, no new matter has been added.

Upon entry of the amendment, claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 78-86 will be pending and subject to further prosecution. Entry of the amendment and reconsideration on the merits in view of the following comments are respectfully requested.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office alleges that new matter was introduced by the replacement of the original nucleotide "B" with nucleotide "G" in SEQ ID NO: 213. The Office states that "[t]he letter 'B' as an IUPAC symbol refers to 5-bromouridine (http://www.chem.gmul.ac.uk/iupac/misc/naabb.html)" and "replacing 5-bromouridine with Guanosine in the nucleotide sequence broadens the scope of the invention and therefore appears to represent a new matter."

As an initial matter, Applicants are perplexed by the Office's referral to the IUPAC nomenclature of nucleotide symbols despite the fact that the MPEP explicitly adheres to WIPO Standard ST.25 (1998). *See* MPEP § 2422, *citing* 37 C.F.R. § 1.821. According to the WIPO nomenclature, the nucleotide symbol "B" corresponds to "G" or "C" or "T/U" (i.e., not "A"). *See* WIPO Standard ST.25 (1998), Appendix 2, Table 1, *reproduced in* MPEP § 2422. Consequently,

contrary to the Office's position, replacing a "B" with a "G" does not represent new matter.

Nevertheless, to advance the prosecution of this application, Table 1 is amended herein to recite the original sequence of SEQ ID NO: 213. Additionally, submitted herewith is a substitute sequence listing in ASCII .txt format via EFS-Web in compliance with 37 C.F.R. §1.821(c) and §1.8215(a) and (b). No new matter has been added. Entry of the substitute sequence listing into the above-captioned application is respectfully requested.

In the view of the foregoing, Applicants respectfully aver that the claims 1, 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 77-80 are supported by adequate written description, and therefore this rejection under 35 U.S.C. § 112, first paragraph may properly be withdrawn.

Rejections under 35 U.S.C. § 103

1) Claims 1, 4, 9, 22, 24, 26, 28, 30-31, 37, 43, 46, 49, 53, 57-60 and 77-79 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Apple *et al.* (US 5,567,809, hereinafter "Apple"), Petersdorf *et al.* (WO 00/79006, hereinafter "Petersdorf"), Samartziduo *et al.* (*Life Sci. News*, 2001, 8:1-3, hereinafter "Samartziduo") in view of Trau *et al.* (*Anal. Chem.*, 2002, 74:3168-3173, hereinafter "Trau").

2) Claims 1 and 7 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Apple, Petersdorf, Samartziduo and Trau, as applied to claim 1 as above, and further in view of Patterson *et al.* (US 5,843,640, hereinafter "Patterson").

3) Claims 1 and 41 are rejected under § 35 U.S.C. § 103(a) as allegedly being unpatentable over Apple, Petersdorf, Samartziduo and Trau, as applied to claim 1 as above, and further in view of Straus (U.S. Patent Pub. No. 2002/0086289, hereinafter "Straus").

4) Claims 1 and 41-42 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Apple, Petersdorf, Samartziduo, Trau and Straus, and further in view of Delenstarr *et al.* (U.S. Patent Pub. No. 2002/0051973, hereinafter "Delenstarr").

5) Claims 1 and 80 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Apple, Petersdorf, Samartziduo and Trau, as applied to claim 1 as above, and further in view of Stockton *et al.* (U.S. Patent Pub. No. 2002/01875505, hereinafter "Stockton").

Applicants respectfully traverse these rejections for the reasons of record and for the additional reasons set forth below.

As an initial matter, claim 1 has been amended to specify that the recited oligonucleotide probe complementary to the target HLA nucleotide sequence must have 30 nucleotides or less and comprise a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1-214 or a complementary strand thereof. Since each of claims 4, 7, 9, 22, 24, 26, 28, 30, 31, 37, 41-43, 46, 49, 53, 57-60 and 78-86 depends, directly or indirectly, from claim 1, all of these claims necessarily incorporate the new limitations as well.

The Office acknowledges that Apple does not teach chip comprising a combination of probes consisting of SEQ ID NOS: 1-214. To cure this deficiency of Apple, the Office cites Petersdorf, which teaches a method for HLA typing of both class I and II alleles comprising oligonucleotide arrays for high resolution HLA typing comprising probes representing 98% of the known polymorphisms of the HLA class 1 locus. Petersdorf also teaches that the probes have at least 90% identity with HLA Class I target gene and further teaches array comprises at least 137 or at least 3,000 different oligonucleotide probes for HLA. The Office asserts that the combined teachings of Apple and Petersdorf provide a chip comprising probes for HLA-A, HLA-A, B and DRB loci up to 98% of the known polymorphisms. Accordingly, the Office concludes that the claimed SEQ ID NOS: 1-214 are obvious over the cited prior art, absent secondary considerations. *See* the OA at pages 9-10, emphases in the original.

Notably, the Office does not assert that Petersdorf disclose any of SEQ ID NOS: 1-214. Instead the Office argues that SEQ ID NOS: 1-214 are rendered obvious over Petersdorf's generic disclosure of "98% of the known polymorphisms of the HLA class 1 locus." Applicants respectfully submit that this constitutes erroneous application of the law.

It is well settled that a determination of patentability under 35 U.S.C. 103 should be made upon the facts of the particular case in view of the totality of the circumstances. MPEP § 2144.08, citing *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990) (en banc). Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103. MPEP § 2144.08, citing *In re Brouwer*, 77 F.3d 422, 425, 37 USPQ2d 1663, 1666 (Fed. Cir. 1996); *In re Ochiai*, 71 F.3d 1565, 1572, 37 USPQ2d 1127, 1133 (Fed. Cir. 1995); *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994). The fact that a claimed species or subgenus is encompassed by a prior art genus is **not sufficient by itself** to establish a *prima facie* case of obviousness. MPEP § 2144.08, citing *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994) ("The fact that a claimed compound may be encompassed by a disclosed generic formula does not by itself render that compound obvious."); *In re Jones*, 958 F.2d 347, 350, 21 USPQ2d 1941, 1943 (Fed. Cir. 1992) (Federal Circuit has "decline[d] to extract from *Merck [& Co. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir. 1989)] the rule that... regardless of how broad, a disclosure of a chemical genus renders obvious any species that happens to fall within it.").

In the case of a prior art reference disclosing a genus, Office personnel should make findings as to: (A) the structure of the disclosed prior art genus and that of any expressly described species or subgenus within the genus; (B) any physical or chemical properties and utilities disclosed for the genus, as well as any suggested limitations on the usefulness of the genus, and any problems alleged to be addressed by the genus; (C) the predictability of the technology; and (D) the number of species encompassed by the genus taking into consideration all of the variables possible. MPEP § 2144.08.

The present claims as amended are drawn to methods of HLA typing that involve the use of one or more oligonucleotide probe(s) comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS: 1-214. The genus disclosed in Petersdorf includes 98% of known polymorphisms of the HLA class 1 locus, which encompasses hundreds of nucleotide sequences of various degrees of similarity that were known as of Petersdorf's priority date (June 17, 1999). At that time, a total of 475 Class I HLA alleles with official names were reported (*see* Bodmer *et al.*,

"Nomenclature for Factors of the HLA System, 1998," *Vox Sang.*, 1999, 77: 164-191, attached herein as ***Exhibit A***, at page 166, left col.). The present application was filed in 2003 and discloses nucleotide sequences that were not known at the time the Petersdorf application was filed. Given the high variability and unpredictability of Class I HLA alleles, a person skilled in the art could not have reasonably envisioned the nucleotide sequences of SEQ ID NOS: 1-214 based on the HLA-B sequences disclosed in Petersdorf or the Class I alleles known at the time of Petersdorf's invention.

Additionally, Applicants note that Petersdorf discloses nucleotide arrays for high resolution HLA typing, which contain groups of highly redundant probes having minor differences in their sequences, often as little as one nucleotide (*see, e.g.*, Petersdorf at pages 17-23, Tables 1 and 2). In contrast, the present invention is concerned with medium resolution HLA typing (*see, e.g.*, WO 2005/001123 at page 31, lines 23-25). The distinction between these two types of genotyping is explained in an article co-authored by three of the co-inventors of the present invention (Zhou *et al.*, "Probe selection algorithm for oligonucleotide array-based medium-resolution genotyping," *Med. Biol. Eng. Comput.* (2004) 42: 812-816, attached herein as ***Exhibit A***):

> Although high-resolution genotyping, which is used to distinguish each target from the others in a group of targets, is needed, medium-resolution genotyping is more popular in the actual practice of tissue typing, taxonomy, disease diagnosis or other target discrimination. **Medium-resolution genotyping, aimed at distinguishing one subgroup from other subgroups, is more attractive, considering the cost, efficiency, factual requirement of the experiment and the present capacity of typing techniques.**
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> (Zhou *et al.* at page 812, right col., emphasis added).

Moreover, as indicated in the Zhou article, the authors had developed a proprietary algorithm that allowed them to select optimal oligonucleotide probe sets for medium resolution HLA-A and HLA-B typing (*see* Zhou *et al.* at pages 813-814). As a result of this optimized probe selection, CapitalBio Corp., which is a co-assignee of the present application, is currently one of the world leaders in HLA genotyping, as described in the enclosed document "HLA Genotyping Services" (*available at* http://www.capitalbio.com/services/genotyping/hla_genotyping_services,

attached herein as ***Exhibit B***). As explained in this document, CapitalBio's sequence-specific oligonucleotide (SSO) probe sets provide exceptional quality HLA genotyping, with an accuracy exceeding 99%.

In view of the foregoing, it is readily apparent that the presently claimed methods are not rendered obvious over Petersdorf's generic disclosure of chip-based high resolution HLA typing. Moreover, none of the other cited references contains any teaching or suggestion that would compensate for this deficiency of Petersdorf. Accordingly, Applicants respectfully submit that the Office has failed to establish a *prima facie* case of obviousness, and therefore this rejection under 35 U.S.C. § 103(a) may properly be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. **514572001200**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 27, 2009

Respectfully submitted,

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